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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,903	11/26/2003	Harry M. Meade	GTC-53	2943

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,903	MEADE ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-63 is/are pending in the application.

4a) Of the above claim(s) 64-89 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-63 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~9/26/5002~~ 2005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-63, drawn to a method of producing an antibody in the milk of a transgenic mammal, classified in class 800, subclass 7.

II. Claims 64-88, drawn to composition of milk comprising an antibody produced by a transgenic mammal, classified in class 424, subclass 535.

III. Claim 89, drawn to a nucleic acid encoding and antibody, classified in class 536, subclass 23.1.

The inventions are distinct, each from the other because of the following reasons:

1.1. Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the antibody can be produced by recombinant technologies in bacteria, yeast or in a hybridoma as a monoclonal antibody and then reconstituted with a milk component.

1.2. Inventions I and III are distinct. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are biologically different materials with different

functions and compositions. The nucleic acid of III serves in cellular protein production, in this instance the production of an antibody, where as the composition of a milk component and the antibody are secreted products of a cell that are chemically different from the nucleic acid (protein, lipid, carbohydrate, etc... but not nucleic acid).

1.3. Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the nucleic acid of III can be used to transfect and be expressed in a mammary cell in vitro.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Byron Olsen on October 20, 2005 a provisional election was made with traverse to prosecute the invention of I, claims 1-63. Affirmation of this election must be made by applicant in replying to this Office action. Claims 64-89 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

2. Claims 1-63 are under consideration.

3. ***Information Disclosure Statement***

The information disclosure statement filed 10/26/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Kabat et al. 1991 is listed as a reference on page 3 of 5 in the IDS, but a copy of this reference was not provided. This reference has not be considered and therefore has been crossed out.

FR 2,487,642 on page 1 of 5 in the IDS was not considered because it was in French and therefore has been crossed out. Also EP 467,482 B1 in the IDS was not considered because it could not be obtained.

4. ***Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures.***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.82(a)(1)

and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for reason(s) set forth on the attached .Notice To Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CRF 1.821(d), which states:

"[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application."

The specification discloses nucleotide and amino acid sequences on pages 33 and 34 of the Specification. However, these sequences are not identified by sequences identifiers.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify then with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing" (see MPEP 2422.03).

For response to this office action to be complete, Applicants are required to comply with the Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence. The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

5. ***Claim Objection***

Claims 33-61 objected to under 37 CFR 1.75(c) as being in improper form because claims 33, 40, 44, 48 are dependent claims that refer to themselves and therefore do not refer to correct independent claims. As a result, dependent claims 33-61 are also misdirected to the wrong claims as well. See MPEP § 608.01(n). Correction of dependent claims to refer to correct claims would be remedial.

6. *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-63 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 5,827,690 in view of U.S. Patent No. 5,849, 992.

The instant invention is drawn to a method of producing antibodies in the milk of a transgenic mammal, wherein the antibody consists of an exogenous heavy chain variable region, at least one heavy chain constant region, and a modified hinge region operable linked to a promoter that directs mammary specific expression of the

transgene (claims 1, 32, 62, 63). Further embodiments include light chain constant and variable regions (claims 3, 34, 62, 62) and specify the modifications to the hinge region as being: (1) a replacement of serine 241 in the hinge region to a proline residue (claims 21, 22, 50, 51); (2) an alteration in at least one glycosylation site in the heavy or light chains or the hinge region (claims 24-26, 53-55); (3) at least one replacement of any amino acid in the hinge region with a cysteine residue (claims 23, 52); or (4) replacement of the whole hinge region of an IgG4 isotype with the hinge region of another isotype (claims 19, 20, 48, 49). Further specifying claims identify the promoter as being a casein, α-lactalbumin, β-lactoglobin, or whey acid protein promoter (claims 6, 35) and specify that the transgenic mammal be a cow, goat, mouse, rat, sheep, pig, or rabbit (claims 7, 36). It also specifies that the milk be obtained from the transgenic mammal (claim 4) and be purified from the milk (claim 5).

Meade et al. (Pat # 5,827,690) also a claims a high level expression method for providing a heterologous and assembled immunoglobulin produced in the milk of a transgenic mammal (claims 1, 8). Although the claims do not specify specific modifications to the immunoglobulins as in the instant invention, claims 1 and 8 are written broadly enough that they encompass any heterologous and assembled antibodies modified or not. As seen in the instant invention, Meade et al. also specifies that the transgenic mammal be mice, sheep, goats, or pigs (claims 2,8) that have constructs encoding for heavy and light chains of human origin (claims 4,5,10,11) and that contain β-lactoglobulin, α-lactalbumin, casein, or whey acid protein promoters

(claims 3,7,9,13). It further specifies that the immunoglobulins be purified from the milk (claims 6, 12).

In the instant invention, claim 1 is drawn to a method of first *providing* a transgenic mammal that produces antibodies in their milk. Mead et al. (Patent # 5,849,992) provides a transgenic mammal that capable of producing antibodies in their milk. Again, the invention described in 5,849,992 does not specify a modified antibody as does the instant invention, but the claims are written broadly enough that modified antibodies are encompassed in those claims.

Since only one patent per invention can be issued and the patents exist that disclose the same invention, the above claims of the instant invention are rejected for obvious-type double patenting.

Furthermore, claims 2-31 and 33-61 are dependent on claims 1 and 32. Since claims 1 and 32 have been rejected for obvious-type double patenting, all dependent claims are also rejected.

7. *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-63 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Above claims are drawn to "transgenic

mammal" which encompasses humans. Humans are considered non-statutory subject matter. Amendment to recite "non-human mammal" will be remedial.

8. *Claim Rejections - 35 USC § 112*

8.1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-63 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing modified antibodies in the milk of a transgenic cow, goat, mouse, rat, sheep, pig, or rabbit, comprising providing a non-human transgenic mammal whose somatic and germ cells comprise a sequence encoding a mutation selected from the list: (1) a replacement of serine 241 to a proline in an IgG4 hinge region; (2) an alteration that eliminates a N-linked glycosylation site on the CH2 of an IgG heavy chain by replacing an asparagine to a glutamine in the consensus site; (3) a replacement of an amino acid in the hinge region with a cysteine residue; and (4) replacement of the entire hinge region of an IgG4 isotype with the hinge region of another IgG isotype and is operabley linked to a milk specific promoter that directs expression to mammary epithelial cells, does not reasonably provide enablement for making a transgenic mammal producing any modified antibody of any class or subclass, assembled or not assembles, in any transgenic mammal's milk. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

In the instant invention, the various claimed mutations to antibodies produced by site directed mutagenesis (procedure described in example 1, p.33) were chosen specifically for their ability to aid the production of whole assembled antibodies in the milk of transgenic mammals. Applicants further describe in example 2 (p 39 lines 10-12) the use of these mutations that result in fewer half antibodies being produced in the milk of transgenic mice carrying sequences that encode these mutations (p.44, lines 18-27 and table 4, p.46).

An artisan when using/making this invention should be able to apply the information found in the specification or apply techniques well established in the art to reproducibly produce antibodies in the milk of a transgenic mammal and obtain a

greater percentage of assembled antibodies. If an artisan were to use or make this invention using anything other than the mutations described in the working examples, they would have to determine a sequence that may provide an alteration to the antibodies that are favorable for producing assembled antibodies, apply these sequences to the expression system as described in the instant invention and determine the amount, if any, of assembled antibodies they obtain. This would require an undue amount of experimentation of on the part of the artisan and therefore producing antibodies in the milk of transgenic mammals with any other sequences than those described in examples 1 and 2 are not enabled.

The instant invention also claims providing or producing a transgenic mammal that produces modified antibodies in their milk. The state of the art at the time of the invention demonstrates that expression of transgenes in the mammary gland and milk of dairy livestock, pigs, mice, rats, and rabbits had been established (Pollock et al. J Immunol Methods 231:p. 150, Table 1, 1999). At the time of invention, no other mammals were successfully being used to express transgenes in their mammary glands and milk, therefore at the time of invention, an artisan would only be able to make or use the instant invention in dairy livestock, pigs, mice, rats, and rabbits. Making or using the instant invention in other mammals at the time of invention would require establishing first that a transgenic mammal other than the above could be produced and then optimizing with the instant invention. This level of experimentation would be considered undue and therefore the instant application is only enabled for transgenesis in dairy livestock, pigs, mice, rats, and rabbits.

In the instant application, one embodiment of the claimed invention provides a transgenic animal by providing a cell from a transgenic mammal to produce a transgenic mammal, but it does not describe to what the cell will be provided to make a transgenic animal, what cells will be provided. Will these cells be introduced into an embryo or used for nuclear transfer? The specification sheds some light on the details of the provided cells and that they can be used in forming embryos but no information about nuclear transfer methodology or the introduction of cells to embryos have been provided in the specification. Because the methodology of nuclear transfer and cell transfer have not been described , an artisan would not know how to use or make this invention without undue experimentation and therefore producing a transgenic by providing a cell from a transgenic is not enabled.

8.2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32, 62, and 63 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: introduction of said cell into an embryo or microinjecting a construct into an embryo, transplantation of the embryo, birth of a potential transgenic mammal, and screen said mammal for transgene expression.

Claims 63 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to a method that involves "providing a cell"

from a transgenic mammal. Which cell is to be provided? Not all cells are capable of being used to make a transgenic animal, therefore, without specifying which cell of interest, this claim is considered vague and indefinite and therefore rejected under 112, second paragraph.

Claims 32, 62, and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method that introduces "into a mammal a construct ". A construct cannot be introduced into a mammal directly. It must be introduced into an embryo or cell transferred into an embryo. For these reasons, this claim is considered vague and indefinite and therefore rejected under 112, second paragraph.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is drawn to a "nucleic acid residues of the nucleic acid sequence encoding the hinge region of the antibody *differs* from naturally occurring nucleic acid sequence ....." The term "differs" does not specifically describe how the two sequences are change and to what extent they are changed. For these reasons, this claim is considered vague and indefinite and therefore rejected under 112, second paragraph.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is drawn to a replacing, "an amino acid

corresponding to that position in an antibody other then an IgG4 antibody". What is meant by corresponding to that position in an antibody? To what is position referring? Because the meaning of this phrase is not easily discernable and interpreted, this claim is considered vague and indefinite and therefore rejected under 112, second paragraph.

Claims 30, 31, 59, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to "half molecules" or half forms of the antibody". Nowhere in the specification or claims has a half antibody been defined therefore the mean is not easily discernable and subject to misinterpretation. For these reasons, this claim is considered vague and indefinite and therefore rejected under 112, second paragraph.

9. *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9.1. Claims 1, 23, 32, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al (Patent # 5,827,690, Oct 27, 1998) in view of Taylerson et al (Patent # 5,985,281, Nov 16, 1999). The instant invention is drawn to a method of producting of antibodies in the milk of a transgenic mammal where in the antibody has an altered hinge region. More specifically in claims 23 and 52, these alterations are defined as a replacement of any amino acid in the hinge region with a cysteine residue. Meade et al teach the production of antibodies in the milk of transgenic mammals but does not teach specifically of producing an antibody with added cysteine residues to the hinge region. Talyerson et al. teach the modification of a recombinant murine $F(ab')_2$ fragment of antibody A5B7 which adds replaces amino acids in the hinge region with cysteine residues (col 10, par 3). Taylerson et al. does not teach the production of recombinant antibodies in the milk of transgenic mammals. Taylerson et al also teach a motivation for such an alteration suggesting that the addition of cysteine residues is necessary for good dimmer formation in recombinant production of antibodies (col 10, par 3, lines 4-10). Meade et al teaches a need for expression systems in which important therapeutic, diagnostic, and industrial immunoglobulins can be reproducible manufactured at high levels, in a functional configuration, and in a form that allows them to be easily harvested and purified. Meade further teaches that this need can be met by transgenic mammals that produce these important molecules in their milk (col 1, par 3).

At the time of invention, it would have been obvious to an artisan of ordinary skill to modify the methods of Meade et al., a high expression method of producing immunoglobulins in the milk of transgenic non-human mammals, with the method of Talyerson et al., a genetic alteration adding cysteine residues to the hinge region of an immunoglobulin. Both Meade et al. and Taylorson provide motivation for the described alteration of immunoglobulins to promote the production of stable and assembled antibodies and produce them in high quantities. Furthermore, it also would have been obvious to an artisan of ordinary skill to use the described genetic modification to immunoglobulins in this high expression system with a reasonable expectation of success because both genetic alteration of immunoglobulins and expression of transgene in the milk of mammals have been successfully demonstrated both in Meade et al and Taylorson et al and other examples in the art.

9.2. Claims 1, 21, 32, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al (Patent # 5,827,690, Oct 27, 1998) in view of Owen et al (Patent Application # US 6,204,007, March 20, 2001). The instant invention is drawn to a method of producing of antibodies in the milk of a transgenic mammal where in the antibody has an altered hinge region. More specifically in claims 21 and 50, these alterations are defined as a replacement of a serine residue in the hinge region with a proline residue. Meade et al teach the production of antibodies in the milk of transgenic mammals but does not teach specifically of producing an antibody with serine to proline replacement in the hinge region. Owen et al. teach the production of an antibody to E-selectin that has a replacement of serine 228 with a proline in its hinge region (col 31,

claim 1). Owen et al. does not teach the production of recombinant antibodies in the milk of transgenic mammals. Owen et al also teach a motivation for such an alteration suggesting that a serine to proline replacement in the hinge region of IgGγ4 isotype will prevent the formation of alternate forms of the antibody (col 4, lines 42-49). Meade et al teaches a need for expression systems in which important therapeutic, diagnostic, and industrial immunoglobulins can be reproducible manufactured at high levels, in a functional configuration, and in a form that allows them to be easily harvested and purified. Meade further teaches that this need can be met by transgenic mammals that produce these important molecules in their milk (col 1, par 3).

At the time of invention, it would have been obvious to an artisan of ordinary skill to modify the methods of Meade et al., a high expression method of producing immunoglobulins in the milk of transgenic non-human mammals, with the method of Owen et al., a genetic alteration replacing a serine with a proline in the hinge region of an immunoglobulin. Both Meade et al. and Owen et al. provide motivation for the described alteration of immunoglobulins to promote the production of stable, consistent antibody with the same isotype (i.e.-no alternative isotypes) and produce them in high quantities. Furthermore, it also would have been obvious to an artisan of ordinary skill to use the described genetic modification to immunoglobulins in this high expression system with a reasonable expectation of success because both genetic alteration of immunoglobulins and expression of transgene in the milk of mammals have been successfully demonstrated both in Meade et al and Owen et al and other examples in the art.

9.3. Claims 1, 12, 15, 16, 18, 20, 32, 41, 44, 45, 47, 49, and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al (Patent # 5,827,690, Oct 27, 1998) in view of Tan et al. (PNAS 87:162-166, 1990). The instant invention is drawn to a method of producing of antibodies in the milk of a transgenic mammal where in the antibody has an altered hinge region. More specifically in claims 12, 15, 16, 18, 20 and 41, 44, 45, 47, 49, 56-58, the instant invention replaces the hinge region of IgG4 with the hinge region of another antibody isotype or subclass. Meade et al teach the production of antibodies in the milk of transgenic mammals but does not teach specifically of producing an antibody with alternate hinge region replacement. Tan et al teach the recombinant production of a chimeric human IgG4/IgG3 anti-dansyl antibody by replacing the hinge region of the IgG4 antibody with the hinge region of a human IgG3 via site directed mutagenesis (p. 163, Fig 1). Tan et al. does not teach the production of recombinant antibodies in the milk of transgenic mammals. Tan et al also teaches motivation for such alteration in that these types of alterations to the hinge region can alter the antibodies binding flexibility and binding affinity for complement which is useful in tailor therapeutic antibodies for varying binding affinity and biological activity (see abstract, p 162). Meade et al teaches a need for expression systems in which important therapeutic, diagnostic, and industrial immunoglobulins can be reproducible manufactured at high levels, in a functional configuration, and in a form that allows them to be easily harvested and purified. Meade further teaches that this

need can be met by transgenic mammals that produce these important molecules in their milk (col 1, par 3).

At the time of invention, it would have been obvious to an artisan of ordinary skill to modify the methods of Meade et al., a high expression method of producing immunoglobulins in the milk of transgenic non-human mammals, with the method of Tan et al, a genetic alteration replacing the hinge region of an immunoglobulin with that of another isotype or subclass. Both Meade et al. and Tan et al. provide motivation for the described alteration of immunoglobulins to promote the production an immunoglobulin with a more altered flexibility in the hinge region and altered ability to bind to complement and antigen and produce them in high quantities. Furthermore, it also would have been obvious to an artisan of ordinary skill to use the described genetic modification to immunoglobulins in this high expression system with a reasonable expectation of success because both genetic alteration of immunoglobulins and expression of transgene in the milk of mammals have been successfully demonstrated both in Meade et al and Tan et al and other examples in the art.

9.4. Claims 1, 24-26, 32, and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al (Patent # 5,827,690, Oct 27, 1998) in view of Chuang and Morrison (J Immonol 158:724-732, 1997). The instant invention is drawn to a method of producing of antibodies in the milk of a transgenic mammal where in the antibody has an altered hinge region. More specifically in claims 24-26 and 53-55, the instant invention alters glycosylation sites in the heavy, light, or hinge region of the

antibody. Meade et al teach the production of antibodies in the milk of transgenic mammals but does not teach specifically of producing an antibody with serine to proline replacement in the hinge region. Chuang and Morrison teach the elimination of the C region N-linked-glycosylation acceptor sites in IgA via site directed mutagenesis (p.724, abstract). Chang and Morrison also teach a motivation for such alterations in that these mutations in glycosylation will aid in designing IgA with enhanced effector function (p. 725, col 1, lines 7-8). Chuang and Morrison does not teach the production of recombinant antibodies in the milk of transgenic mammals. Meade et al teaches a need for expression systems in which important therapeutic, diagnostic, and industrial immunoglobulins can be reproducible manufactured at high levels, in a functional configuration, and in a form that allows them to be easily harvested and purified. Meade further teaches that this need can be met by transgenic mammals that produce these important molecules in their milk (col 1, par 3).

At the time of invention, it would have been obvious to an artisan of ordinary skill to modify the methods of Meade et al., a high expression method of producing immunoglobulins in the milk of transgenic non-human mammals, with the method of Chuang and Morrison, a genetic alteration changing a conserved glycosylation in an immunoglobulin. Both Meade et al. and Chuang and Morrison provide motivation for the described alteration of immunoglobulins to promote the production an immunoglobulin with enhanced effort function, useful in therapeutics and diagnostics, and produce them in high quantities. Furthermore, it also would have been obvious to an artisan of ordinary skill to use the described genetic modification to immunoglobulins

in this high expression system with a reasonable expectation of success because both genetic alteration of immunoglobulins and expression of transgene in the milk of mammals have been successfully demonstrated both in Meade et al and Chuang and Morrison and other examples in the art.

9.5. Claim 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pollock et al. (J Immuno Methods 231:147-157, 1999) in view of Clark et al. (Biotechnology 7:487-492, 1989).

Claim 4 is drawn to a method comprising steps to obtain milk from a transgenic mammal that produces modified antibodies in their milk of claim 1, to thereby provide an antibody composition. Pollock et al. teach examples of transgenic mammal producing antibodies in their milk (Table 2, p. 152), but do not specifically teach a method of obtaining milk to provide an antibody composition. Clarke et al. teach a method of obtaining milk from transgenic sheep that express human Factor IX in the milk of transgenic sheep (p.491, col 2, lines 10-16). Clarke et al. does not teach the production of antibodies in milk by a transgenic mammal. Pollock et al. also teach motivation to produce antibodies in milk of dairy animal. Pollock et al. teach that production of high levels of immunoglobulin in the milk of transgenic animals can be obtained (p. 155, col 1, par 4, line 1-3) and that this type of expression system is a more efficient way of producing antibodies compared to traditional commercial recombinant antibody production (p. 148, par 3). Furthermore, mammalian transgenic expression provides for glycosylation that is more similar than that using bacteria and yeast to generate

recombinant antibodies with may result in less rejection by patients (p. 155, col 1, par 4, line 4-6).

At the time of invention, it would have been obvious to an artisan of ordinary skill to modify the methods of Pollock et al., a high expression method of producing immunoglobulins in the milk of transgenic non-human mammals, with the method of Clarke et al, a method of obtaining milk from transgenic. Pollock et al provide motivation for obtaining milk from a transgenic mammals as obtaining a highly produced valuable protein. Furthermore, it also would have been obvious to an artisan of ordinary skill to use the milking methods described in Clark et al. to obtain milk from transgenic mammals with a reasonable expectation of success because the milking of animals has been done for centuries.

9.6 Claim 1 and 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kutzko et al. (US Patent # 6,268,487, July 2001) in view of Pollock et al. (J Immuno Methods 231:147-157, 1999). Claim 5 of the instant invention is drawn to a method of purifying the exogenous antibody from the milk produced by a transgenic mammals of claim 1. Kutzko et al. teaches a method of purifying biologically active proteins from milk. More specifically they teach a method of extracting monoclonal antibodies from the milk of transgenic goats (col 12, example 4). Kutzo et al. does not teach a method that specifically addresses the genetic modifications to antibodies discussed in the instant application. Pollock et al. also teach motivation to produce antibodies in milk of dairy animal. Pollock et al. teach that production of high levels of immunoglobulin in the

milk of transgenic animals can be obtained (p. 155, col 1, par 4, line 1-3) and that this type of expression system is a more efficient way of producing antibodies compared to traditional commercial recombinant antibody production (p. 148, par 3). Furthermore, mammalian transgenic expression provides for glycosylation that is more similar than that using bacteria and yeast to generate recombinant antibodies with may result in less rejection by patients (p. 155, col 1, par 4, line 4-6).

At the time of invention, it would have been obvious to an artisan of ordinary skill to use the methods of Kutzko et al. in the instant, a method of purifying antibodies from the milk of transgenic goats in the instant application. Pollock et al provide motivation for purifying the exogenous antibody from the milk of a transgenic mammals as obtaining a highly produced valuable protein. Furthermore, it also would have been obvious to an artisan of ordinary skill to use the milking methods described in Kutzko et al. to purify the exogenous antibody from the milk of transgenic mammals with a reasonable expectation of success because the method of Kutzko et al previously has been used with transgenic mammal milk and similar techniques have been well established in the art.

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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